severe or diffuse PAVMs. However, a cohort study of 219 consecutive patients with HHT and PAVMs showed no clear relationship between the risk of brain abscess or stroke with markers of PAVM severity, including diameter of the largest feeding vessel or degree of right-to-left shunt. As mentioned by Dr Salerno, a second potential mechanism has to do with the local microenvironment at the pulmonary vasculature level. The extensive accumulation of pulmonary intravascular macrophages that adhere to the pulmonary endothelium in animal models of biliary cirrhosis is very well known and is believed to be a compensatory mechanism due to the dramatic decrease in the phagocytic capacity of the liver that allows circulating bacteria to enter the pulmonary circulation. If a similar phenomenon occurs in humans, we speculate that the increased intravascular macrophage activity could play a role in better bacterial clearance, despite shunting. A third potential mechanism is the common use of antibiotic therapy to prevent spontaneous bacterial peritonitis in patients with HPS compared with patients with HHT. Long-term antibiotic use in these patients may help to further reduce transient bacteremia, decreasing the risk of brain abscesses. Furthermore, it has been shown in experimental models that the use of antibiotics, such as norfloxacin (commonly prescribed in patients with cirrhosis to prevent spontaneous bacterial peritonitis), reduces the severity of intrapulmonary shunting by decreasing the nitric oxide production of the pulmonary intravascular macrophages. We agree with Dr Salerno that further prospective studies which include the reporting of cerebrovascular events in the setting of HPS are needed to elucidate this important clinical question.

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References

Evidence Roflumilast Reduces Severe Exacerbations?

To the Editor:

In the May 2013 issue of CHEST, Wedzicha et al conclude in the abstract section of their article that the reduction in severe exacerbations leading to hospitalization or death associated with roflumilast was similar between subgroups defined as infrequent and frequent exacerbators. This is misleading, as it implies there is a reduction in severe exacerbations associated with roflumilast. The datasets published in this article report the number of patients who experienced infrequent exacerbations (zero or one) or frequent exacerbations (two or more) with roflumilast vs placebo. Although listed as a study end point, there are no data presented illustrating the number of patients experiencing severe exacerbations to support the claim that there is a reduction in severe exacerbations associated with roflumilast. The authors state that in patients defined as frequent exacerbators in the year prior to study, there is a reduction in severe exacerbations associated with roflumilast. The authors also observed a significant reduction in severe exacerbations leading to hospitalization or death associated with roflumilast.

In the pivotal study by Calverley et al there was a reduction in the combined end point of moderate/severe exacerbations in roflumilast compared with placebo (1.14 vs 1.37, P < .0003). However, a closer look at the data reveals that there was no difference in severe exacerbation rate (0.12 vs 0.15, P = .334), indicating that the improvement in the combined end point is truly an improvement in the rate of moderate exacerbation alone. I believe it is important that the effect of roflumilast on severe exacerbations of COPD be reported accurately by Wedzicha et al as previously published data do not provide evidence that roflumilast prevents severe exacerbations of COPD.

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Response

To the Editor:

We would like to thank Dr Coyle for his interest in our recent article in CHEST. We apologize that the sentence included in the abstract, stating that the reduction in severe exacerbations leading to hospitalization/death was similar between subgroups, lacked clarity.

We presented pooled post hoc data on the effects of a 1-year treatment with roflumilast or placebo on exacerbation frequency in subsets of patients with either frequent (two or more) or infrequent (only one) exacerbations in the previous year (year 0). Among frequent exacerbators, roflumilast significantly lowered the risk for those remaining in the frequent exacerbator group by 20% compared with placebo (risk ratio [RR], 0.799; P = .0148). When looking at the proportion of patients with frequent severe exacerbations (two or more) at year 1 in the subgroup of frequent exacerbators, the risk reduction with roflumilast vs placebo was 46.6%; however, the effect missed statistical significance (RR, 0.534; 95% CI, 0.28-1.00; P = .0516). The wide CI is mainly attributable to the small subgroup experiencing severe COPD exacerbations, that is, 3.4% (roflumilast) and 6.5% (placebo) of the frequent exacerbator subgroup. Similarly, the 18% reduction of severe COPD exacerbations observed with roflumilast vs placebo in two 1-year studies failed to meet statistical significance (RR, 0.82; 95% CI, 0.63-1.06; P = .1334). Bateman et al.1 investigated the effects of roflumilast on the number of hospitalizations resulting from severe COPD exacerbations based on data from the same two 1-year trials using negative binomial regression analysis. Because of the small number of severe COPD exacerbations (annual rate per patient, 0.16 and 0.126 for placebo and roflumilast, respectively), this statistical analysis is considered more appropriate than the Poisson regression model presented in the article by Calverley et al.2 Compared with placebo, roflumilast decreased the rate of hospitalizations resulting from severe COPD exacerbations by −21.6% (RR, 0.784; 95% CI, 0.619-0.993; P = .0439).

In conclusion, data suggest a consistent trend with borderline statistical significance in the reduction of severe COPD exacerbations with roflumilast vs placebo in patients with severe to very severe COPD. We express our sincerest respect to Dr Coyle for having initiated this discussion.

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